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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/031,289	05/31/2002	Vega Masignani	PP01639.102; 2300-1639	6882

7590 10/04/2005

Chiron Corporation
Intellectual Property Department R440
PO Box 8097
Emeryville, CA 94662-8097

EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,289	MASIGNANI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,10 and 25-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 06/23/05 in response to the non-final Office Action mailed 01/21/05. With this Applicants have amended the specification.

Applicants cite sections 1850 and 1893.03(d) of MPEP and argue that claims 9 and 17 be examined with the elected polypeptide claims. As set forth clearly in paragraph 3 of the written lack of unity mailed 05/07/04, the lack of unity was properly established under PCT Rule 13.1 and 13.2. Paragraph 4 of the written lack of unity mailed 05/07/04 clearly stated the reason that the nucleic acid of invention II (i.e., the second product claimed) does not share significant structural features with the polypeptide product of invention II. Therefore, claims drawn to the first claimed product are examined. As set forth in paragraph 4 of the written lack of unity, the first claimed product was disclosed in the prior art. However, since Applicants have elected the product claims of invention I, the method of using these product claims would be kept pending pursuant to the rejoinder provisions of M.P.E.P 821.04 and would be rejoined with the elected product claims if and when the product claims are deemed allowable. In the event of rejoinder, the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. To be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. *Failure to do so may result in a loss of the right to rejoinder.*

Status of Claims

2) Claim 1 has been amended via the amendment filed 06/23/05.

Claims 1, 7, 9, 10, 13, 15, 17, 19, 21 and 23-33 are pending.

Claims 1, 10 and 25-32 are under examination.

Prior Citation of Title 35 Sections

3) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

4) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

5) The objection to the specification made in paragraph 7 of the Office Action mailed 01/21/05 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

6) The rejection of claim 1 and those dependent therefrom made in paragraph 9 of the Office Action mailed 01/21/05 under 35 U.S.C § 101 as being directed to a non-statutory subject matter, is withdrawn in light of Applicants' amendment to the claim.

7) The rejection of claim 1 and those dependent therefrom made in paragraph 10 of the Office Action mailed 01/21/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claim. A modified rejection is set forth below.

8) The rejection of claims 1, 10 and 25-32 made in paragraph 11 of the Office Action mailed 01/21/05 under 35 U.S.C. § 112, first paragraph, as containing inadequate written description, is withdrawn upon further consideration.

9) The rejection of claim 1 made in paragraph 14(a) of the Office Action mailed 01/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claims 10 and 25-32 made in paragraph 14(b) of the Office Action mailed 01/21/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

11) The rejection of claims 1 and 25-28 made in paragraph 16 of the Office Action mailed

01/21/05 under 35 U.S.C § 102(b) as being anticipated by Relf *et al.* (*J. Clin. Microbiol.* 30: 3190-3194, 1992), is withdrawn in light of Applicants' amendment to the base claim.

12) The rejection of claims 10 and 29-32 made in paragraph 18 of the Office Action mailed 01/21/05 under 35 U.S.C § 103(a) as being unpatentable over Relf *et al.* (*J. Clin. Microbiol.* 30: 3190-3194, 1992) as applied to claim 1 or 25, is withdrawn in light of Applicants' amendment to the base claim.

13) The rejection of claims 1, 10 and 25-32 made in paragraph 12 of the Office Action mailed 01/21/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn. It is noted that Applicants have amended claim 1 with regard to % identity and have added a functional limitation. In view of this, a new rejection is set forth below to reject the claims, as amended.

Response to Applicants' Arguments

14) Applicants traverse the lack of scope of enablement rejection made in paragraph 12 of the Office Action mailed 01/21/05 under 35 U.S.C. § 112, first paragraph. Applicants cite *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) and state that the first paragraph of § 112 requires nothing more than objective enablement and how such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance. Applicants state that unless there is reason to doubt the objective truth, the statements contained in a specification disclosure must be relied on for enabling support. Applicants further submit the following arguments: (a) Undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, the references cited by the Examiner do not in any way establish unpredictability. When the *Wands* factors are considered, it is clear that the specification as filed fully enables the pending claims throughout their scope. (b) Claim 1, as amended, does not require that the antigenic polypeptides have all the functional or biological properties of the native protein from which the fragment, SEQ ID NO: 1331 was obtained. A correlation between polypeptide structure (primary sequence or tertiary structure) and immunogenic function indicates that antigenic polypeptides can tolerate many modifications. (c) Applicants are under no legal obligation to teach each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as a whole are sufficient to

establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. See e.g., U.S. Patent and Trademark Office's Training Materials on Enablement, p. 29. (d) Given the information provided by SEQ ID NO: 1331 on page 2, lines 10-13, one of skill in the art would be able to routinely identify a polypeptide comprising a contiguous amino acid sequence with at least 70% sequence identity to the sequence of SEQ ID NO: 1331. At the time of filing of the instant application, determining sequence identity was utterly routine. Furthermore, the specification also provides guidance on how to make the claimed polypeptide variants. For example, the specification at page 2, lines 18-22, describes how to make the polypeptides by recombinant expression or chemical synthesis. The identification of relevant polynucleotides encoding the variant polypeptides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed. See, e.g., page 34, line 10 through page 35, line 25 and page 36, lines 26-33. (e) The specification further provides guidance on methods of identifying antigenic polypeptides e.g., page 37, lines 9-29, and methods of using antigenic polypeptides to produce antibodies (e.g., page 21, line 5 through page 22, line 18), in immunogenic compositions such as vaccines (e.g., page 23, line 25 through page 25, line 15), and in immunodiagnostic assays e.g., page 33, line 27 through page 34, line 8. Thus, the specification provides ample guidance as to methods of identification, generation, and use of the antigenic polypeptides of the claimed invention. (f) The cited references of Burgess *et al.*, 1990; Lazar *et al.*, 1988; and Bowie *et al.*, 1990 allegedly establishing the unpredictability of the art are not relevant to the claimed subject matter. The claimed antigenic variant polypeptides are not required to retain all the functional or biological properties of the native protein, but rather, are only required to have antigenic function, that is, the ability to elicit an immune response against Neisserial bacteria. Sequences that do not produce antigenic polypeptides that elicit an immune response to Neisserial bacteria are not encompassed by the claims. (g) It is not necessary to predict a protein's structure in order to elicit an immune response to a protein. Contrary to the Office Action's assertions, production of antibodies to an antigen is routinely practiced in the absence of knowledge of a protein's structure. (h) Applicants further submit the following arguments:

> One of skill in the art can routinely produce antibodies that specifically bind to a protein by immunizing an appropriate host with oligopeptide fragments of that protein. It is well known in the art that it is possible to produce antibodies to almost any part of an antigen, and is not especially difficult to obtain antibodies with specificity for a particular protein. The specification provides sufficient guidance for one of skill in the art to elicit an immune response with the recited antigenic polypeptides. See specification, e.g., at pages 21-22, and

page 33, line 27 through page 34, line 4.

(i) It is well settled that time-consuming or expensive experimentation is not undue if it is routine. The possibility of generating inoperative embodiments, allegedly established by the cited references discussed above, is not relevant to the claimed invention. (j) The presence of inoperative embodiments does not necessarily render a claim nonenabled. The test of enablement is not what is predictable *a priori*, but what the specification teaches the skilled practitioner in regard to the claimed subject matter. Thus, not every species (or even a majority of species) encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976. The notion that one of ordinary skill in the art must have reasonable assurances of obtaining positive results on every occasion has been emphatically rejected. So long as it is clear that some species render the claims operative, the inclusion of possible inoperative species cannot invalidate the claim under paragraph 1 of 35 U.S.C. 112. Every single polypeptide species exhibiting 70% identity to SEQ ID N0: 1331 can be determined *a priori* and, as such, the entire genus of polypeptides exhibiting 70% identity to SEQ ID NO: 1331 is enabled by the specification as filed. (k) There is no requirement under the law to provide working examples. A prophetic example describes an embodiment of the invention based on 'predicted' results rather than work actually conducted or results actually achieved. One looks to whether the specification provides a description of how to make and use what is claimed. The present specification provides the requisite description. (l) The Examiner has failed to provide any reasons why one would doubt that the guidance provided by the present specification would enable one to make and use the recited meningococcal polypeptides. Hence, a *prima facie* case for non-enablement has not been established.

Applicants' arguments have been carefully considered, but are not persuasive. Applicants may be correct in that one of skill in the art can routinely produce antibodies that specifically bind to a protein by immunizing an appropriate host with oligopeptide fragments of that protein. However, production of antibodies that specifically bind to a particular protein by immunizing a host with a 'variant' that has at least 30% non-identity to an oligopeptide fragment of that particular protein is not predictable. In the instant application, the lack of scope of enablement rejection is set forth because there is reason to doubt the objective truth. The present specification provides the requisite description for the polypeptide fragment having the SEQ ID NO: 1331. However, the instant

specification does not provide the requisite enabling disclosure as to how to make and use the at least 70% identical polypeptide variant that is being claimed which variant has the recited function of eliciting 'an immune response against Neisseria bacteria'. The statements contained in the instant specification with regard to polypeptides with at least 70% identity (i.e., polypeptide variants) have been relied on for enabling support. However, the absence of a concrete showing combined with what was known in the art at the time of the invention with regard to the functional unpredictability associated with polypeptide variants in general, and meningococcal polypeptide variants in particular, render these statements insufficient for enablement of the full scope of the claimed invention. The immunogenicity of the claimed at least 70% identical polypeptide variant is not the issue, but its immunospecificity to 'Neisserial bacteria' is.

Claim 1, as amended, requires that the purified polypeptide variant having at least 70% sequence identity to SEQ ID NO: 1331 'comprise at least one antigenic determinant that elicits an immune response against Neisserial bacteria'. The generic limitation 'Neisserial bacteria' encompasses many species, serogroups, serotypes, subtypes, and immunotypes of pathogenic and commensal *Neisseriae*. This includes *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Neisseria lactamica*, *Neisseria sicca*, *Neisseria cinerea* etc. Contrary to Applicants' assertion, there is absolutely no showing of a correlation between the primary or tertiary structure of a polypeptide that is at least 30% non-identical to SEQ ID NO: 1331 and its immunogenic function(s) as recited. There is no showing that these polypeptide variants tolerate many modifications and remain antigenic and immunogenic with respect to neisserial bacteria. The claims are not enabled throughout their full scope. Applicants are correct in that they have no legal obligation to teach each and every member of the claimed genus. However, in the instant application, not even a single operative polypeptide variant species or member (let alone a majority of the species) having at least 30% non-identity to SEQ ID NO: 1331 is shown to 'elicit an immune response against Neisserial bacteria'. In the instant case, a skilled artisan would not expect the claimed genus to be used in the manner set forth. There is not one single showing within the instant specification that a polypeptide when varied to have 30% non-identity to SEQ ID NO: 1331 would retain the ability to elicit an immune response against any neisserial bacteria, homologous or heterologous *Neisseria* and pathogenic or non-pathogenic *Neisseria*. When this lack of enabling disclosure is evaluated together with what was known about

amino acid variations or substitutions in polypeptides in general, or meningococcal polypeptides in particular, the propriety of lack of scope of enablement becomes self-evident.

The law with regard to the unpredictability factor is clear. The predictability or unpredictability is a *Wands* factor, which cannot be dismissed in the face of what is evident from the state of the art on amino acid variation in a peptide. MPEP 2164.03 [R-2] sets forth the relationship of predictability of the art and the enablement requirement. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The 'amount of guidance or direction' refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004). The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated: [I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based

thereon for proof. [Footnote omitted.] In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In the instant case, it is not obvious from the disclosure of unmodified SEQ ID NO: 1331, what other variant species thereof would work. Thus, the case law pertaining to unpredictability actually requires something more concrete than the mere allegation that the references cited by the Office do not in any way establish unpredictability. The *Wands* unpredictability factor has been sufficiently established previously using the teachings of Bowie *et al.*, Burgess *et al.*, and Lazar *et al.* and would not be repeated herein. With particular reference to a meningococcal polypeptide, two publications, McGuinnes *et al.*, 1991 and McGuinnes *et al.*, 1993, demonstrate that a single amino acid change (let alone 30% non-identity) within an epitope (i.e., antigenic determinant), and an amino acid deletion even outside an epitope, were both associated with 'loss of subtype specificity' and striking changes in the structural and immunological properties of the meningococcal class 1 outer membrane protein. See paragraph 16 below.

Given this art-recognized unpredictability, the specification lacks precise guidance or teaching as to how to make a representative number of at least 70% identical polypeptide variants that would retain the antigenic determinant having the ability to elicit an immune response against any neisserial bacteria. The specification does not teach where to effect one or more than one substitutions, within an antigenic determinant of SEQ ID NO: 1331 or outside such an antigenic determinant such that it retains the recited function. Applicants have not enabled a single (let alone a representative number) at least 70% identical polypeptide variant of SEQ ID NO: 1331 that comprises an antigenic determinant which elicits an immune response against any generic neisserial bacteria. Given the art-recognized unpredictability associated with structure-function relationship, one of skill in the art would look into the specification for specific teaching and guidance, which in the instant

case is lacking. The courts have held that it is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement. Such is the case in the instant application. In view of the art-recognized unpredictability specifically with regard to a meningococcal polypeptide, the lack of specific teachings and guidance in the specification, and the breadth of the claims, undue experimentation would have been required on the part of the skilled artisan to practice the full scope of the invention as claimed. See paragraph 16 below for a detailed analysis.

New Rejection(s) based on Applicants' Amendment

The new rejections set forth below are necessitated by Applicants' amendments to the claims.

Rejection(s) under 35 U.S.C § 112, First Paragraph (New Matter)

15) Claim 1 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, now includes the limitations: 'purified' polypeptide comprising a contiguous amino acid sequence with at least '70%' sequence identity to 'the sequence of' SEQ ID NO: 1331, wherein the polypeptide ..... elicits an immune response against Neisserial bacteria' and has a length of 100 amino acids or less. Applicants state that lines 7-10 on page 2 of the specification provide descriptive support for the new limitations. However, this part of the specification is not supportive of a purified polypeptide having 70% sequence identity to the amino acid sequence of SEQ ID NO: 1331 and concurrently having an antigenic determinant that has the ability to 'elicit an immune response against' the generically recited 'Neisserial bacteria'. Lines 7-10 on page 2 of the specification do not associate any function to the at least 70% identical polypeptide variant. Furthermore, the term 'Neisserial bacteria' encompasses any species, serogroup, serotype, or subtype of pathogenic or non-pathogenic *Neisseria*, for which there is no support in the specification as

originally filed. Therefore, the above-identified limitation in the claim(s) is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the newly added limitation(s), or remove the new matter from the claim(s).

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

16) Claims 1, 10 and 25-32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a purified fragment of a meningococcal protein wherein the fragment has the amino acid sequence of SEQ ID NO: 1331, does not reasonably provide enablement for a polypeptide that has a length of 20, 25, 50, or 100 amino acids or less and comprises a contiguous amino acid sequence with 'at least 70% sequence identity to SEQ ID NO: 1331', wherein the polypeptide comprises at least one antigenic determinant 'that elicits immune response against Neisserial bacteria', as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims, as amended, encompass a purified polypeptide fragment comprising a contiguous amino acid sequence with at least 70% sequence identity to the 18 amino acid-long amino acid sequence, SEQ ID NO: 1331, wherein the purified polypeptide fragment has a length of 100, 50, 25 or 20 amino acids or less and comprises at least one antigenic determinant 'that elicits immune

response against Neisserial bacteria'. The generic limitation 'Neisserial bacteria' is so broad that it encompasses many species, serogroups, serotypes, subtypes, and immunotypes of pathogenic and commensal *Neisseriae*. This includes at least *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Neisseria lactamica*, *Neisseria sicca*, *Neisseria cinerea* etc. and those neisseria bacteria yet to be discovered. The limitation 'polypeptide .... comprising a contiguous amino acid sequence with at least 70% sequence identity to the sequence of SEQ ID NO: 1331' encompasses purified polypeptides comprising contiguous amino acid sequences with at least 30% non-identity to the sequence of SEQ ID NO: 1331. The specification indicates diagnostic applications as well as therapeutic and vaccination (prophylactic) intentions. See lines 17-19 and 28-30 of page 3; line 13 of page 4 of the specification; section 'Immunodiagnostic Assays' on pages 33 and 34 of the specification; and section 'Vaccines' on pages 23-25 o the specification. The 'antigenic determinant' is described as including B-cell epitopes and T-cell epitopes (see line 7 of page 5 of the specification). The claimed product is intended for use as an agent that treats, ameliorates or prevents a desired disease (see lines 20-25 of page 22 of the specification). In other words, the recited polypeptide variant having at least 70% non-identity with the amino acid sequence of SEQ ID NO: 1331 is *required* to have the antigenic determinant which elicits an immune response against any neisserial bacteria. The diagnostic, therapeutic and prophylactic applications described in the specification indicate that the claimed composition comprising the at least 30% non-identical polypeptide variant is meant for use in diagnosis, treatment, or prevention of 'neisserial' infections. However, there is not one single showing within the instant specification that a polypeptide when varied to have at least 30% non-identity to SEQ ID NO: 1331 would retain the ability to elicit an immune response against any neisserial bacteria, homologous or heterologous, and pathogenic or non-pathogenic. Not a single polypeptide variant species (let alone a representative number of variant species) having at least 30% non-identity to SEQ ID NO: 1331 is shown to 'elicit an immune response against Neisserial bacteria'. The claims are not enabled throughout their full scope. There is absolutely no showing of a correlation between the primary or tertiary structure of a polypeptide that is at least 30% non-identical to SEQ ID NO: 1331 and its immunogenic functions. There is no showing that these polypeptide variants tolerate many modifications and remain antigenic and immunogenic with respect to 'neisserial bacteria'. With this lack of showing, the Office would look into the literature in the

relevant art of polypeptide variants in order perform the required *Wands* analysis. A review of the state of the art at the time of the invention, particularly with regard to unpredictability as associated with meningococcal proteins reveals the following. The art shows that an alteration in a single even amino acid can eliminate or drastically change one or more function(s) of the polypeptide. For instance, McGuinnes *et al.* (*Lancet* 337: 514-517, March 1991) showed that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). With particular reference to VR1 and VR2 epitopes of Class 1 outer membrane protein of *Neisseria meningitidis*, McGuinnes *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993) also taught that "[a] single amino acid change *within an epitope*, or an amino acid deletion *outside an epitope*, were both associated with *loss of subtype specificity* resulting from a change in the predicted conformation at the apex of the loop structure" (see abstract) [Emphasis added]. One of skill in the art can reasonably expect a loss of immunospecificity to 'neisserial bacteria' in Applicants' polypeptide variant which has as much as 30% non-identity to the amino acid sequence of SEQ ID NO: 1331. It should be noted that Applicants have neither identified a functional site, i.e., neisserial bacteria-specific antigenic determinant that elicits an immune response against any generic neisserial bacteria, in a single polypeptide variant that is 70% identical to the amino acid sequence of SEQ ID NO: 1331, for one of skill in the art to avoid or to include mutation(s) or variation(s) within or outside the antigenic determinant. The lack of disclosure and specific guidance within the instant specification combined with the art-recognized functional unpredictability would require one of skill in the art to engage in considerable undue experimentation.

Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences (i.e., fragments), or even in different positions of the same sequence (see page 3). The lack of guidance within the instant specification in

combination with Rudinger's teachings support the Office's position regarding the unpredictability factor and the need to engage in considerable undue experimentation.

The state of the art on microbial polypeptides in general indicates that a random replacement affecting the epitopic amino acid positions that are critical to the three-dimensional conformational structure and specific binding property of a protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool. [Emphasis added]

Thus, it has already been established in the art that variations in critical residues at specific positions of an amino acid sequence could result in a polypeptide variant, which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In other words, although a polypeptide having as much as 30% non-identity to the native polypeptide is likely to be immunogenic, there is no predictability that such a variant would remain immunospecific to any neisserial bacteria.

The above-cited references reasonably demonstrate that even a single amino acid substitution/deletion will often dramatically affect the immunospecific biological activity or characteristics of a protein. Clearly, with as much as 30% non-identity to the polypeptide of SEQ ID NO: 1331, the neisserial bacteria-specific immunogenic function of the claimed polypeptide variants cannot be predicted, merely based on the sequence similarity or identity with SEQ ID NO: 1331, nor would it be expected to be nearly the same as that of the polypeptide of SEQ ID NO: 1331. This is particularly so because even the unmodified polypeptide that is 100 amino acids or less in length that comprises SEQ ID NO: 1331 has not been shown to contain an antigenic determinant that elicits an immune response against the broadly recited 'Neisserial bacteria'. Although a skilled artisan might envision making a number of changes in the reference polypeptide sequence of SEQ ID NO: 1331 in

accordance with Applicants' disclosure, it is highly uncertain that the polypeptide variant as recited would acquire 'at least one antigenic determinant that elicits an immune response against Neisserial bacteria' as recited. Furthermore, if one nucleotide in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 1331 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 1331. For these reasons, making and using of the instantly claimed polypeptide variant having the recited ability to elicit an immune response against Neisserial bacteria is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the neisserial art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

17) Claims 1, 10 and 25-32 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 lacks proper antecedent basis in the limitation: 'the sequence of SEQ ID NO: 1331' (see line 3) without clearly reciting that SEQ ID NO: 1331 is the amino acid sequence. Since the claim already includes the limitation 'the amino acid sequence of SEQ ID NO: 1331', it is suggested that Applicants replace the limitation with --the amino acid sequence of SEQ ID NO: 1331--.

(b) Claims 10 and 25-32, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Remarks

18) Claims 1, 10 and 25-32 stand rejected.

A purified polypeptide 100 amino acids or less in length wherein the polypeptide comprises the

amino acid sequence of SEQ ID NO: 1331, and a composition comprising the same and a pharmaceutically acceptable carrier, are free of prior art currently of record.

19) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses and papers is (571) 273-8300.

20) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2005

S. DEVI, PH.D.
PRIMARY EXAMINER